REMARKS/ARGUMENTS

In response to the Office Action of November 18, 2004, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claim 1 has been amended. Claims 2-38 have been cancelled. New claims 39-46 have been added. Claims 1 and 39-46 remain pending in the instant application.

If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the peptides of claim 1.

No new matter has been added by the amendments to claim 1 made herein.

Claim 1 has been amended to incorporate the subject matter of cancelled claim 2. Claim 1 has also been amended to indicate that the claimed peptides are isolated from their natural state, and thus are not considered "products of nature" (see page 20, lines 9-16 of the instant specification). The claimed peptides have been identified with sequence identification numbers.

No new matter has been added by the addition of new claims 39-

46. The subject matter of new claims 39-46 corresponds with subject matter of original claims 2-38 (now cancelled). New claims 39-46 also find support in the original specification, at page 25, line 16 to page 26, line 22.

The instant specification as originally filed contains explicit support for all of the newly added claims (39-46). Page 46, lines 6-15 and Figures 1-4 indicate that the claimed peptides are linked to Alzheimer's disease. The method of new claim 39 is described in detail at pages 37-47. Page 48, lines 1-5 refers to various types of samples that may be tested for the presence of the claimed peptides. Page 38, line 22 to page 39, line 2 refers to the numerous mass spectrometric techniques which can be used to carry out the claimed methods. Page 46, line 22 to page 47, line 2 refers to practicing the claimed methods with samples obtained from human patients. Page 36, lines 9-12 indicate that an objective of the invention is to provide diagnostic kits containing the reagents necessary to practice the claimed methods. Pages 47-48 describe the kits contemplated. Page 47, line 19 to page 48,line 1 refers particularly to the immobilizing on solid supports and labeling of components of the contemplated kits.

Thus, it is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated

by the inventors at the time of filing and are enabled by virtue of the disclosure as originally filed.

No new matter has been added by the amendments to the specification made herein.

The title of the application has been amended to correct a punctuation error in the spelling of Alzheimer's (Alzheimers corrected to recite Alzheimer's).

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23 per request of the Examiner.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to clearly indicate that Figures 2 and 4 show the mass spectrum profiles of the claimed peptides; Figure 2 is SEQ ID NO:1 and Figure 4 is SEQ ID NO:2. The descriptions of Figures 1 and 3 have also been amended to correct a punctuation error in the spelling of Alzheimer's (Alzheimers corrected to recite Alzheimer's).

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The titles at page 41 (lines 8 and 22), page 42 (line 14) and page 43 (lines 4 and 18) were underlined in the original disclosure and

have not been amended.

The paragraph at page 46 has been amended to correct a punctuation error in the spelling of Alzheimer's (Alzheimers corrected to recite Alzheimer's). The claimed peptides have also been identified with sequence identification numbers. The paragraph was also amended to remove the (-) symbol shown in SEQ ID NO:2.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 13 in order to provide proper support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation in the biochemical art for cerebrospinal fluid. A typographical error within the same paragraph was also amended; skill replaced skilled.

The abstract has been amended to remove the legal phraseology ("said").

Restriction/Election

Applicants herein affirm the election of Group I (original claims 1 and 2) for prosecution on the merits. The election was made, with traverse, during a telephone conference between Ferris Lander and the Examiner on August 6, 2004.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NOS:1 and 2, a search of these claims would encompass these specific peptides. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptides of SEQ ID NOS:1 and 2 are found to be novel, methods and kits limited to their use should also be found novel.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statement filed on March 12, 2002 has been considered as to the merits prior to the first action.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statement provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Applicants have not received a copy of the PTO-1449 filed on March 12, 2002 initialed by the Examiner indicating that the references have been considered and indicating whether the citation is in conformance with MPEP 609.

Applicants hereby request that a copy of this PTO-1449 form be sent out with the next Office communication.

Prior Amendments

Applicants respectfully submit that the Office has not entered two documents previously submitted by Applicants into the prosecution file of the instant application; a Preliminary Amendment mailed on March 4, 2002 and a Response to a Notice to

Comply mailed on August 16, 2002.

Applicants previously submitted a Preliminary Amendment, mailed on March 4, 2002, which was stamped received by the Patent and Trademark Office on March 8, 2002, see attached copy of stamped postcard. This Preliminary Amendment was filed concurrently with the Response to the Notice to File Missing Parts. The Preliminary Amendment included changes to the specification at page 46 appropriately identifying sequences with sequence identification numbers. The Preliminary Amendment also included a separate paper copy of the Sequence Listing and an electronic form of the Sequence Listing identical to the paper copy of the Sequence Listing.

Applicants received a Notice to Comply, mailed on August 8, 2002, indicating that a computer-readable form of the Sequence Listing had not been submitted as required by 37 CFR 1.821(e). At that time Applicants resubmitted a separate paper copy and computer-readable form of the Sequence Listing in compliance with the requirements under 37 CFR 1.821-1.825. A copy of the postcard stamped received on August 20, 2002 is also enclosed.

Considering that these prior documents are not in compliance with the current format for Amendments, the instant Response is based upon the specification and claims as originally filed.

Oath/Declaration

A new oath or declaration has been required by the Examiner because the original oath, filed on November 23, 2001, is not signed by the inventors.

Applicants filed an oath with the Response to the Notice to File Missing Parts (mailed on March 4, 2002). The postcard, returned by the Patent and Trademark Office to provide confirmation of receipt of documents, was stamped March 8, 2002.

However, upon review of the oath received at the PTO on March 8, 2002, it was noted that while the second inventor signed the oath, he did not date his signature.

Applicants are currently in the process of preparing a new oath and will forward such oath to the Examiner as soon as it is completed and properly executed.

Objections to the Specification

The Examiner notes that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors.

The Examiner points out a typographical error at page 1, line 23, in which parentheses were not closed in the text. The instant specification has been amended to correct this and other similar kinds of errors.

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE at page 41, lines 2 and 3 and TRITON at page 42, line 10) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 40-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Sequence Compliance

The Examiner asserts that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner notes that the application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The Examiner asserts that the disclosure contains sequences that have not been appropriately identified by sequence identification numbers at page 46.

The Examiner has requested that Applicant return a copy of the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures with the Response to the Office Action mailed on November 18, 2004; however, Applicants note that no such Notice (form PTO-1661) was attached to the Office Action.

Applicants herein provide a Sequence Listing in both paper and computer-readable form. The computer-readable form of the Sequence Listing is identical to the paper form of the Sequence Listing. The sequences listed in the Sequence Listing have been identified as SEQ ID NOS: 1 and 2 and are disclosed at page 46 of the originally filed specification, thus the Sequence Listing, in both paper and

computer-readable form, contains no new matter.

The instant specification has been amended at page 46 to include sequence identification numbers for the amino acid sequences disclosed at lines 11 and 14.

Applicants respectfully submit that the instant application is now in compliance with the sequence requirements of 37 CFR 1.821-1.825. However, should the Sequence List (paper and disk copies) not be found fully in compliance with all requirements, Applicants respectfully request prompt notice by telephone in order to accomplish expedite correction within the term allotted.

Objection to the Claims

The Examiner has objected to claims 1 and 2 under 37 CFR 1.821(d) for failing to recite SEQ ID NOS in the claims.

Claim 2 has been cancelled and claim 1 has been amended to identify the claimed peptides by sequence identification numbers; SEQ ID NOS:1 and 2. The claims added herein (39-36) also properly recite sequence identification numbers.

Applicants respectfully submit that the instant claims are now in compliance with 37 CFR 1.821(d) and respectfully request that the objection to the claims now be withdrawn.

Rejection under 35 USC 101

Claims 1 and 2, as originally presented, stand rejected under USC 101 as allegedly being directed to non-statutory subject matter. The Examiner states that the biopolymer markers of SEQ ID NOS: 1 and 2, or any analyte thereof reads on naturally occurring protein.

Claim 2 has been cancelled and claim 1 recites two biopolymer marker peptides (SEQ ID NOS:1 and 2).

A peptide naturally present in a living organism, i.e. a "product of nature", is not considered "isolated", but the same peptide separated from the co-existing materials of its natural state is considered "isolated". The claimed biopolymer marker peptides (SEQ ID NOS:1 and 2) have been isolated from their natural state in living human patients and thus are not considered "products of nature". An explanation of how the term "isolated" is employed in the instant specification can be found at page 20, lines 9-16.

Claim 1 has been amended to indicate that the claimed biopolymer marker peptides are isolated from their natural state.

Applicants respectfully submit that the pending claims are drawn to patentable subject matter and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Double Patenting

Claims 1 and 2, as originally presented, stand rejected under 35 USC 101 as allegedly claiming the same invention as that of claims 1 and 2 of co-pending application number 09/993,304. Since neither set of allegedly conflicting claims have been patented, the claims are provisionally rejected under statutory double patenting.

The Examiner states that SEQ ID NO: 1 of 09/993,304 is the same as SEQ ID NO: 2 in the instant application.

It is noted that claims 1 and 2, as originally presented, are provisionally rejected under the judicially created doctrine of non-statutory double patenting of the obviousness type and barred under 35 USC 101, the statutory basis for a double patenting rejection. When a double patenting rejection is deemed appropriate, it must be based on either statutory grounds or non-statutory grounds, see MPEP 804 (II).

Applicants respectfully submit that the rejection of claims 1 and 2 should properly based upon non-statutory double patenting, since the there is an embodiment (i.e. SEQ ID NO: 1) present in claim 1 of the instant application that does not fall within the scope of claim 1 in the co-pending application 09/993,304, thus "identical" subject matter is not defined by both claims and statutory double patenting would not exist. See MPEP 804 II(A). Applicants will respond as if it is a proper non-statutory

rejection, however, clarification by the Examiner is requested.

The peptide of co-pending application 09/993,304 (SEQ ID NO:1) comprises amino acid residues XSVLTQPPSVSGAPGQR(V), the same peptide of the instant invention (SEQ ID NO:2). On December 6, 2004, Applicants filed a response to the restriction requirement, which included a species election, in co-pending application 09/993,304. Claim 1 was amended to recite only elected SEQ ID NO: 3 for prosecution on the merits. The scope of the claims in co-pending application 09/993,304 now encompass only this specific peptide (SEQ ID NO:3) which is patentably distinct from the claimed peptides of SEQ ID NOS: 1 and 2 of the instant invention.

Accordingly, Applicants have clarified that the pending claims of the instant application are in fact patentably distinct from the claims of co-pending application 09/993,304 and thus respectfully request that this rejection under 35 USC 101 (double patenting) now be withdrawn.

Rejections under 35 USC 112, second paragraph

Claims 1 and 2, as originally presented, stand rejected under 35 USC 112, second paragraph as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claims 1 and 2 are vague and

indefinite because it is unclear as to what the phrase "at least one analyte thereof" is intended to define. The claim is directed to biopolymers consisting of SEQ ID NOS: 1 and 2. However what is considered an analyte of SEQ ID NOS:1 and 2 is not defined by the claims or the specification. The Examiner asserts that as such the metes and bounds of the claims cannot be determined and one of ordinary skill in the art would not be appraised of the scope of the invention.

Applicants respectfully disagree with the Examiner's assertions. The instant specification indicates what the term "analyte" is meant to define at page 6, lines 15-23. However, in the interest of compact, efficient prosecution, Applicants have amended the claims to remove recitation of the phrase "at least one analyte thereof".

The Examiner also asserts that claims 1 and 2 are vague and indefinite because the biopolymer is "indicative" of at least one particular disease state in claim 1 and "predictive" of Alzheimer's disease in claim 2. "Indication" and "predictability" are relative terms, which render the claims indefinite. The terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner further asserts that it is not clear

as to how the measurement of the biopolymer marker will serve to indicate a particular disease state or predict Alzheimer's disease.

Applicants respectfully disagree with the Examiner's assertions. The instant specification defines the terms "indicative" and "predictive" in relation to a disease state at page 11, lines 9-20 and further discloses how the measurement of the biopolymer marker will serve to indicate a particular disease state or predict Alzheimer's disease. However, in the interest of compact, efficient prosecution, Applicants have amended the claims to remove recitation of the terms "indicative" and "predictive".

The Examiner additionally asserts that it is not clear as to how the marker will identify Alzheimer's disease because a correlation of the markers with Alzheimer's disease is not disclosed in the specification.

Applicants respectfully disagree with the Examiner's assertion. Claim 2 has been cancelled. Claim 1 has been amended to clearly recite an isolated biopolymer marker peptide (SEQ ID NO:1 or SEQ ID NO:2)which is diagnostic for Alzheimer's disease. Figures 1 (SEQ ID NO:1) and 3 (SEQ ID NO:2) demonstrate that these biopolymer marker peptides are present in body fluid samples obtained from Alzheimer's disease patients but are not present in body fluid samples obtained from patients age-matched with the Alzheimer's disease patients. Thus, a qualitative correspondence

i.e. correlation, exists between the two comparable samples. Furthermore, the language of claim 1 indicates that a correlation exists between the presence of the biopolymer marker peptides (SEQ ID NOS:1 and 2) and the diagnosis of Alzheimer's disease. According to Webster's Third New International Dictionary, the term "diagnostic" means "serving to distinguish, determine or identify". Keeping within this definition, the specification discloses that an objective of the instant invention is to provide a diagnostic kit for determining the presence of a disease specific marker (see page 36, lines 9-12). It is clear from this context that the term "diagnostic" refers to the identification of a disease-specific marker.

Thus, Applicants respectfully submit that, contrary to the Examiner's assertions, it is clear as to how the marker will identify Alzheimer's disease because a correlation of the markers with Alzheimer's disease is disclosed in the specification.

The Examiner asserts that claim 1 is further vague and indefinite because it is not clear as to what the symbol (-) is intended to mean. The symbol is included in the amino acid sequence consisting of (-)XSVLTQPPSVSGAPGQR(V).

Applicants respectfully disagree with the Examiner's assertion. The symbol (-) is conventionally known as a place marker for an amino acid residue which is present in the predicted

sequence but is not actually identified as present in the experimental results. However, in the interest of compact, efficient prosecution, Applicants have amended the amino acid sequence within the claims and the specification to remove the symbol (-).

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejections under 35 USC, 112, second paragraph be withdrawn.

Rejection under 35 USC 112, first paragraph

Claims 1 and 2, as originally presented, stand rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 2 are directed to biopolymers consisting of SEQ ID NO:1 and 2 indicative of Alzheimer's disease. The Examiner asserts that the specification does not support this assertion. The specification (in particular page 46) and the figures do not definitely correlate the claimed markers consisting of SEQ ID NOS:1

and 2 to Alzheimer's disease. The Examiner asserts that the specification recites that biopolymers consisting of SEQ ID NOS:1 and 2 were found in the serum of patients suffering from Alzheimer's disease on page 46 but does not contain any data supporting this contention and the figures do not identify SEQ ID NOS:1 and 2. Therefore, the Examiner contends it is unclear how SEQ ID NOS:1 and 2 were identified as "notable sequences" or how they were deemed "evidentiary" of a disease state. The Examiner asserts that there is nothing in the disclosure that would enable one to choose SEQ ID NO: or 2 as notable sequences among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

The decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Claim 2 has been cancelled and claim 1 has been amended to clearly recite an isolated biopolymer marker peptide (SEQ ID NO:1 or SEQ ID NO:2)which is diagnostic for Alzheimer's disease.

At page 46, lines 9-11, SEQ ID NO:1 (marker(Y14737)) immunoglobulin heavy chain is identified as having a molecular

weight of about 1287 daltons. At page 46, lines 12-13, SEQ ID NO:2 (marker(X91133) immunoglobulin lambda chain variable region is identified as having a molecular weight of about 1694 daltons. The description of Figure 2 at page 37 indicates that the ion 1287 is depicted in the spectra. Additionally, the molecular weight (1287 daltons) is labeled on the right side of the spectra shown in Figure 2. Ion 1287 is known to be SEQ ID NO:1 based upon the information disclosed at page 46 of the instant specification. The description of Figure 4 at page 37 indicates that the ion 1694 is depicted in the spectra. Additionally, the molecular weight (1694 daltons) is labeled on both right and left sides of the spectra shown in Figure 4. Ion 1694 is known to be SEQ ID NO:2 based upon the information disclosed at page 46 of the instant specification. The spectra in Figure 2 is labeled AD-H-S-S1 (scrub)C3; indicating that this spectra was obtained from band 3 of the scrub gel shown in Figure 1; thus SEQ ID NO:1 was obtained from band 3 (resolved from a sample obtained from an Alzheimer's patient) as shown in the gel of Figure 1. The spectra shown in Figure 4 was obtained from band 2 (resolved from a sample obtained from an Alzheimer's patient)as shown in the gel of Figure 3. The descriptions of the figures have been amended to clarify that the data shown in the figures is representative of the claimed SEQ ID NOS:1 and 2.

Figures 1 (SEQ ID NO:1) and 3 (SEQ ID NO:2) demonstrate that

these biopolymer marker peptides are present in body fluid samples obtained from Alzheimer's disease patients but are not present in body fluid samples obtained from patients age-matched with the Alzheimer's disease patients. Thus, a qualitative correspondence i.e. correlation, exists between the two comparable samples. Furthermore, the language of claim 1 indicates that a correlation exists between the presence of the biopolymer marker peptides (SEQ ID NOS:1 and 2) and the diagnosis of Alzheimer's disease. According to Webster's Third New International Dictionary, the term "diagnostic" means "serving to distinguish, determine or identify". Keeping within this definition, the specification discloses that an objective of the instant invention is to provide a diagnostic kit for determining the presence of a disease specific marker (see page 36, lines 9-12). It is clear from this context that the term "diagnostic" refers to the identification of a disease-specific marker.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained by the disclosed protocol. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the claimed method. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker

peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describe how biopolymer markers are evaluated according to the methods of the instant invention. Page 46, line 16- page 47,line 10 of the instant specification clearly state that the steps of the invention include obtaining a sample from a patient and conducting a MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol. Further, Applicants assert that such information can be found in the art.

Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to

view a gel, such as that shown in Figure 1 from which one of the claimed peptides was identified (SEQ ID NO:1), and recognize a difference between two comparable samples(disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 1 is a gel showing the results of HiS resin (cation exchanging) column chromatography as carried out with a set of 9 samples; 4 serum samples from Alzheimer's disease patients (lanes 1-4, as read from the left), 4 serum samples from patients age-matched with the Alzheimer's patients (lanes 5-8, as read from the left) and 1 sample of normal serum (lane 9, as read from the left). Patient serum samples AD-H-S-005 and AD-H-S-006, shown in lanes 2 and 3, respectively, display a band, numbered band 3, from which the claimed peptide was isolated. Patients numbered AD-H-S-005 and AD-H-S-006 are both Alzheimer's disease patients. This band 3 is not present in any of the serum samples from age-matched patients (lanes 5-8, as read from the left) or in the normal serum sample (lane 9, as read from the left).

Additionally, Figure 3 shows a gel similar to that of Figure 1 with the exception of the resin used for the chromatography, DEAE (anion-exchanging resin). Alzheimer's patient serum samples, shown in lanes 2 and 3 from the left, respectively, also displays band

2 (labeled IgG lambda chain) from which one of the claimed peptides (SEQ ID NO:2) was isolated. This band 2 is not present in any of the serum samples from age-matched patients (lanes 5-8, as read from the left) or in the normal serum sample (lane 9, as read from the left).

Contrary to the Examiner's assertions, the instant specification and figures, as originally filed, correlate the claimed markers (SEQ ID NOS:1 and 2) with a diagnosis of Alzheimer's disease. Furthermore, the figures identify SEQ ID NOS:1 and 2 and the specification discloses how such sequences were identified as notable sequences.

Thus, Applicants contend a skilled practitioner would find the data presented in Figures 1 and 3 is convincing with regard to a correlation of the claimed biopolymer marker peptides and Alzheimer's disease.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that there is no correlation between the procedure for screening samples form suspected of having a variety of different disease, the presence/absence of SEQ ID NOS:1 or 2; and the determination, prediction, assessment of at least one particular disease state like Alzheimer's disease. There is no

disclosure enabling the use of the biopolymer markers with regard to regulating the presence or absence of said markers. The disclosure is lacking any teaching for how the identified sequences will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequences could be utilized therein.

Applicants are not required to enable material that is not claimed. The pending claims do not recite any disease state other than Alzheimer's disease, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequences or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that the association of the claimed peptides with Alzheimer's disease is not supported by any evidence of record, rather the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that

something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. Although the prior art does not specifically recognize that claimed SEQ ID NO: 1 or SEQ ID NO: 2 are correlated with Alzheimer's, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease in unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker. When one of skill in the art observes the claimed peptides identified in samples from an Alzheimer's disease patient or differentially expressed between Alzheimer's disease patients and non-diseased patients; one of skill in the art would connect these peptides with potential diagnostics and/or therapeutics for Alzheimer's disease.

Thus, Applicants respectfully submit that since the instant specification demonstrates a correlation between the claimed peptides (SEQ ID NOS:1 and 2) and Alzheimer's disease and that this

correlation connotes the use of the claimed peptides in potential diagnostics and/or therapeutics of Alzheimer's disease, the requirement of "how to use" under 35 USC, 112, first paragraph is satisfied.

The Examiner cites an article Hampel *et al* (Journal of Neural Transmission 111:247-272 2004) which is allegedly relevant to the instant invention. According to the Examiner, Hampel *et al* reports on the difficulty involved in the discovery of marker candidates for Alzheimer's. The Examiner states that several required criteria must be met when determining a marker for Alzheimer's, including; indication of disease progression, heterogeneity of the clinical population, feasibility of testing, assay sensitivity, frequency of assessments, stability, standardization, dynamic range and comparative analysis. The Examiner seems to believe that since the specification allegedly lacks any of the criteria stated in the Hampel *et al* reference, it would require undue experimentation for one skilled in the art to make and use the invention.

Applicants respectfully assert that the criteria suggested by Hampel *et al* do not control the issue of enablement with regard to the instant invention. The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Applicants claim that the presence of a biopolymer

marker peptide (SEQ ID NO:1 or SEQ ID NO: 2)is diagnostic of Alzheimer's disease; a statement which is enabled by the data presented in Figures 1-4. The claimed method involves a simple observation of the presence of the markers (as shown in Figures 1 and 3) in a gel, and conducting mass spectrometry analysis to identify the markers present in the gel. Hampel et al. disclose a study similar to that of the instant inventors; see page 260, last paragraph. In this study the content of body fluid obtained from MCI (mild cognitive impairment) patients was compared with the content of body fluid obtained from normal control patients. The MCI patients showed an elevated level of a protein, p-tau_{231}, in comparison to the healthy control patients. Hampel et al. deemed the results of this study adequate to suggest that high levels of p-tau_{231} may be a predictor for progressive cognitive decline in subjects with MCI. This disclosure of Hampel et al. demonstrates further that when elevated levels of proteins are found associated with a disease state, the protein is considered useful for potential diagnostics and/or therapeutics in the disease condition. Thus, in contrast to the Examiner's assertion, the article of Hampel et al. supports enablement of the instant invention. Based upon the above-discussion, Applicants respectfully submit that compliance with the "required" criteria for a diagnostic assay according to Hampel *et al* is not necessary to show that the instant

invention is enabled. When subjected to the "test for enablement" the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed biopolymer markers with Alzheimer's disease carries with it a connotation of use for diagnostics.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those

marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The first thing noted about the Tockman *et al* reference is the publication date; it was published almost ten years prior to the date of Applicants' invention. Theories and standards in biotechnology change quickly over time and especially over a decade. Thus, the Tockman *et al* reference is not considered to accurately assess the field of the invention at the time of Applicants' invention.

Secondly, the Tockman *et al* article is concerned with early detection of cancer biomarkers and apparently does not discuss biomarkers for Alzheimer's disease. Although both the Tockman *et al* reference and the instant invention are drawn to the identification of biomarkers, they are not considered to be analogous since a direct parallel can not be drawn between the neoplastic disease process and the disease process of Alzheimer's. The Tockman *et al* is further not analogous in the type of markers taught. Tockman *et al* discusses biomarkers for early detection of disease wherein in order to a show a marker for early detection the marker must be present before standard clinical diagnosis of the disease. Applicants identify the claimed biomarkers in the serum of patients with a history of Alzheimer's. Applicants are not

claiming the marker to be present before the pathogenesis or neurodegeneration associated with Alzheimer's occurs, thus it is not necessary to link or validate the marker with confirmation of disease.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05).

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is not enabled.

Based on the considerations noted in the above paragraphs, it is respectfully submitted that the Tockman *et al* and Hampel *et al.* references cited by the Examiner are of negligible importance for evaluating enablement of the instant invention.

In conclusion, Applicants claim that the presence of a biopolymer marker peptide, SEQ ID NO:1 or SEQ ID NO: 2, is diagnostic for Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize how to use the claimed peptides as markers for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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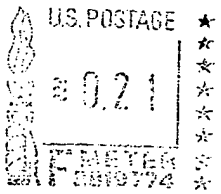

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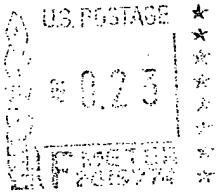

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Examiner 08 4

1: Proc Natl Acad Sci U S A. 1992 Dec 15;89(24):11949-53.

Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker.

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In this report, 8- and 2-azidoadenosine 5'-[gamma-32P]triphosphate were used to examine cerebrospinal fluid (CSF) samples for the presence of an ATP binding protein unique to individuals with Alzheimer disease (AD). A 42-kDa ATP binding protein was found in the CSF of AD patients that is not observed in CSF from normal patients or other neurological controls. The photolabeling is saturated with 30 microM 2-azidoadenosine 5'-[gamma-32P] triphosphate. Photoinsertion can be totally prevented by the addition of 25 microM ATP. Photoinsertion of 2-azidoadenosine 5'-triphosphate into the protein is only weakly protected by other nucleotides such as ADP and GTP, indicating that this is a specific ATP binding protein. A total of 83 CSF samples were examined in a blind manner. The 42-kDa protein was detected in 38 of 39 AD CSF samples and in only 1 of 44 control samples. This protein was identified as glutamine synthetase [GS; glutamate-ammonia ligase; L-glutamate:ammonia ligase (ADP-forming), EC 6.3.1.2] based on similar nucleotide binding properties, comigration on two-dimensional gels, reaction with a polyclonal anti-GS antibody, and the presence of significant GS enzyme activity in AD CSF. In brain, GS plays a key role in elimination of free ammonia and also converts the neurotransmitter and excitotoxic amino acid glutamate to glutamine, which is not neurotoxic. The involvement of GS, if any, in the onset of AD is unknown. However, the presence of GS in the CSF of terminal AD patients suggests that this enzyme may be a useful diagnostic marker and that further study is warranted to determine any possible role for glutamate metabolism in the pathology of AD.

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